Case Report

An autopsy case of non-traumatic fat embolism syndrome

Mai Sakashita,1 Shingo Sakashita,2 Akiko Sakata,3 Noriko Uesugi,2 Kazunori Ishige,4 Ichinosuke Hyodo4 and Masayuki Noguchi2

1Doctoral Program in Biomedical Science, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan, 2Department of Pathology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, 3Department of Pathology, Hitachi General Hospital, Ibaraki, Japan, and 4Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Fat embolism syndrome (FES) occurs after long bone fractures and the symptoms appear 24–72 h after the initial trauma. Fat emboli can affect both the pulmonary and systemic circulation. Apart from the most common type of FES that originates from bone fracture, non-traumatic FES has been also reported. We have experienced an autopsy case of non-traumatic FES. An 81-year-old man with hepatocellular carcinoma associated with alcoholic liver cirrhosis suddenly lost consciousness before transcatheter arterial chemoembolization treatment for his disease and died 5 h after the episode. At autopsy, numerous fat droplets were detected in the alveolar capillaries of the lung and glomerular capillaries of the kidney. Lipid analysis of lung autopsy specimens by thin-layer chromatography showed that the emboli were composed mainly of tristearin. Free fatty acids (FFA) has been considered to be the main component of fat emboli and can be a cause of acute respiratory distress syndrome (ARDS). However, in the present case, the lung specimen contained tristearin and ARDS did not occur. This is the first report of non-traumatic FES in which lipid analysis of human autopsy specimens has been conducted.

Key words: fat embolism syndrome, non-trauma, lipid analysis, phosphatidylcholine, tristearin

On the other hand, non-traumatic FES has also been reported in association with bone marrow necrosis in sickle cell disease,4 corticosteroid administration, fatty liver disease,5 bone marrow transplantation, pancreatitis, liposuction,6 and diabetes mellitus (DM).7 Although FES is characterized by both pulmonary and systemic fat embolism, the biological mechanism of FES has not been clarified in detail.6

We have experienced a case of clinically unexplained sudden death without any trauma in which autopsy revealed numerous fat emboli in multiple organs, including the lung and kidney. We report this autopsy case of non-traumatic FES and describe the results of lipid analysis by thin-layer chromatography using autopsy materials.

CLINICAL SUMMARY

An 81-year-old Japanese man had been diagnosed three years previously as having hepatocellular carcinoma in the hepatic portal region associated with alcoholic cirrhosis. He had undergone proton radiation therapy and the carcinoma had been well controlled. However, a year before the last admission, another hepatocellular carcinoma had appeared in the S7 region for which transcatheter arterial chemoembolization (TACE) had been performed twice. Because of local re-recurrence of the liver carcinoma in S7, he was admitted to the University Hospital of Tsukuba, Japan, for a third session of TACE. On the day of admission, his performance status was good (PS1) and his vital signs were normal. His height was 161 cm and weight was 68.6 kg. Other than mild anemia (hemoglobin 11 g/dL), the laboratory data were unremarkable. Serum lipids levels were within normal limits (triglyceride (TG) 82 mg/dL, phospholipid 168 mg/dL, total cholesterol (TC) 149 mg/dL, high-density lipoprotein cholesterol (HDL-C) 38.4 mg/dL, and low-density lipoprotein cholesterol (LDL-C) 84 mg/dL). The C-reactive protein (CRP) level was 0.79 mg/dL.
In the morning, just after coughing, the patient suddenly lost consciousness on his ward bed and suffered cardiopulmonary arrest (CPA). At that time, TACE was not performed. He had no symptom of a petechial rash. After CPA, the levels of all lipids, especially TG, were decreased (TG, 82 mg/dL on admission and 36 mg/dL after CPA; phospholipid 168 mg/dL and 99 mg/dL; TC, 149 mg/dL and 83 mg/dL; HDL-C, 38.4 mg/dL and 21.7 mg/dL, LDL-C 84 mg/dL and 52 mg/dL, respectively). Computed tomography revealed no signs of injury, and the cause of CPA was unknown. Despite immediate cardiopulmonary resuscitation and percutaneous cardiopulmonary support, the patient died 5 h after the episode. Autopsy was conducted 3 h after death.

PATHOLOGICAL FINDINGS

Macroscopically, the lungs were reddish and their weights were increased (left lung, 550 g; right lung, 780 g) (Fig. 1a). Infarction or hemorrhage was not evident. The kidneys were also reddish and their weights were 140 g (left) and 120 g (right) (Fig. 2a). Infarction or hemorrhage was not evident. The heart weighed 360 g and a patent foramen ovale was not evident. The thickness of the left ventricular wall was 11 mm and that of the right ventricular wall was 4 mm. Right ventricular dilation was not evident. The coronary arteries showed arteriosclerosis. The liver weighed 870 g, and a well-circumscribed tumor was detected in the right lobe (S7). It was 3 cm in diameter and yellowish white in color (Fig. 3a). The tumor was classified as the simple nodular type macroscopically. No tumor was found in the hepatic portal region. The aorta showed severe atherosclerosis.

The autopsy materials were fixed in buffered formalin for 7 days, then hematoxylin and eosin (HE) staining was performed. For oil red O staining, frozen sections from the formalin-fixed samples were prepared. We also performed fat staining using osmium tetroxide by a modification of Mochizuki et al.'s protocol.8 Briefly, specimens were fixed in 10% neutral-buffered formalin and cut to 10 × 10 × 2 mm. They were rinsed in tap water for 3 h and stained with a mixture of 2% osmium tetroxide and 5% potassium dichromate. The specimens were then sealed hermetically and heated at 60°C for 4 h. After rinsing, the samples were embedded in paraffin, cut into sections 3 μm thick, and deparaffinized. After bleaching with 5% periodic acid, HE staining was performed.

Microscopically, both of the lungs were congested but there was no inflammation or diffuse alveolar damage (DAD). Interestingly, numerous alveolar capillaries in both lungs were significantly dilated and empty in all microscopic fields on HE staining (Fig. 1b). In the kidneys, most of the glomerular capillaries were distended diffusely (Fig. 2b,c).

Figure 1 Lungs. (a) Macroscopic findings, (b) HE staining, ×200, (c) Oil red O staining, ×200, (d) Osmium staining, ×200. (a) The lungs are reddish and their weights are increased. Infarction or hemorrhage is not evident. (b) Alveolar capillaries are dilated diffusely in both lungs. (c, d) Intravascular fat is confirmed by oil red O staining and osmium staining.
Oil red O staining and osmium staining revealed numerous fat droplets in both the alveolar and glomerular capillaries (Figs. 1c,d, 2d,e). Moreover, luminal fat particles in blood vessels were detected in the myocardial capillaries of the heart and Glisson capsule in the liver (Fig. 3b). The fat embolism found in the present case was different from bone marrow embolism, since the fat embolism consisted of only adipose cells and there were no accompanying hematopoietic cells. In addition, cholesterol embolisms were not found in any of the organs, although the aorta showed severe atherosclerosis.

The liver showed diffuse cirrhosis (Fig. 3c) and the well-circumscribed liver tumor was histologically diagnosed as moderately differentiated hepatocellular carcinoma (Fig. 3d). The pathological stage of the hepatocellular carcinoma was yaT2N0M0, yaStageII. The liver didn’t show steatosis.

Although the coronary artery showed arteriosclerosis and maximum 75% stenosis, no occlusion was evident. The heart did not show myocardial infarction, and the cardiac conduction system was unremarkable.

The bone marrow showed normal cellularity and there was no evidence of bone marrow necrosis.

As there were no possible causes of death other than systemic fat emboli, we considered that death had been due to non-traumatic FES.

We performed thin-layer chromatography (TLC) to analyze the type of lipid composing the fat droplets found in capillaries. This study was approved by the Ethics Committee of the University of Tsukuba Hospital (H28-162). Although lipid analysis is usually performed using fresh tissues, we used formalin-fixed samples of lung because fresh tissue samples were not available. We were able to extract lipid using the Folch method, and decided to conduct TLC, which was performed at Toray Research Center (Tokyo, Japan). Another autopsy case (a 75-year-old Japanese man who had died due to hemorrhage) was used as a normal control. We analyzed the levels of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), cholesterol (Ch), tristearin (TG), and stearic acid (FFA). The results are shown in Table 1. The levels of PC, TG, and FFA in the patient’s lung samples were 2.47 μg/mg, 3.28 μg/mg and 1.77 μg/mg, respectively, and those in control lung samples were 1.15 μg/mg, 2.60 μg/mg, and 2.83 μg/mg, respectively.
DISCUSSION

We have described a rare case of non-traumatic FES. Previously reported cases of non-traumatic FES are summarized in Table 2.9–18 Although there have been several reports of non-traumatic FES associated with fatty liver,5 this is the first report of non-traumatic FES associated with hepatocellular carcinoma. Schulz et al. reported two cases of fatal fat embolism associated with steatosis,5 and indicated that massive fat embolism could have originated from fatty liver. The liver of the present patient showed cirrhosis, however, there was no evidence of steatosis.

Although many researchers have assumed that FES finally leads to acute respiratory distress syndrome (ARDS),5 our patient did not show DAD in the lungs. In addition, only two out of 16 reported cases with non-traumatic FES had ARDS (Table 2). Therefore, ARDS may not necessarily occur in non-traumatic FES.

Although the exact pathogenesis of FES remains unknown, several theories have been suggested.15 The two main theories are the mechanical theory and the biochemical theory. Since the present patient had not suffered any injury, the mechanical theory could not fully explain the pathogenesis of the present case.

The biochemical theory includes several possible mechanisms. One of them is that release of FFAs is associated with FES.6 Pneumocyte lipases can hydrolyze triglyceride into FFAs, which release toxic substances that damage the capillary endothelium. FFAs increase vascular permeability and inactivate surfactants. Finally, respiratory failure due to ARDS may occur. Lipid analysis of the present autopsied lung sample confirmed that the fat emboli contained...
triglyceride (preliminary observation) (Table 1). In addition, Schinaid et al.\textsuperscript{19} have reported that FFA was only moderately higher in patients with long bone fractures and concluded that mobilization of FFA did not contribute to FES. Moreover, in rat models, Takada et al. have reported that an injection of neutral fat caused fat embolism, however, fat embolisms did not occur with an injection of FFAs. They hypothesized that hyperviscosity of glycerol caused occlusion of capillaries.\textsuperscript{3} We thought that our present results might reflect this mechanism, since the patient's lung samples contained TG (Table 1) and the serum level of TG was decreased significantly after CPA (36 mg/dL, as compared with 82 mg/dL on admission). On the basis of our results and these previous reports, we consider that TG might have been a contributory factor in the present case.

There were several limitations to this study. To our knowledge, there have been no previous reports of lipid analysis using formalin-fixed samples, and thus the variation and reproducibility of this approach has not been validated. In addition, only one control sample was used. Therefore, the present data must be regarded as preliminary, and accumulation of further cases is needed.

Nevertheless, this is the first report of lipid analysis being employed in a case of non-traumatic FES using human autopsy specimens that contained fat emboli (Table 2).

Although Mendoza et al. employed gas chromatography coupled with mass spectrometry to examine oily material between muscle fibers in buttock area since the patient got gluteal injection of vitamin E before death,\textsuperscript{12} the authors did not analyze the organ that contained fat embolism. Moreover, hitherto, lipid analysis of human FES using organ samples which contain fat embolism was conducted only by using bronchoalveolar lavage.\textsuperscript{20} In addition, although several reports have documented animal models of FES created by injecting several kinds of fat, they did not analyze the fat emboli themselves, even in animal autopsy specimens.\textsuperscript{3}

In conclusion, we have reported an autopsy case of non-traumatic FES with lipid analysis of a lung specimen. This confirmed that the emboli contained TG and there was no evidence of DAD in the lungs. These results indicated that this case of non-traumatic FES was caused by numerous lipid emboli containing TG. The biological mechanism of these emboli is still unknown, therefore, accumulation of further cases will help to clarify the pathogenesis of FES.

DISCLOSURE STATEMENT

None declared.

Table 2 Reported cases of non-traumatic fat embolism syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying disease (or precedent medical practice)</th>
<th>Diagnostic tool</th>
<th>Lipid analysis</th>
<th>PFO</th>
<th>ARDS (DAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present case</td>
<td>2017</td>
<td>81</td>
<td>M</td>
<td>Hepatocellular carcinoma</td>
<td>Autopsy</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cantu CA, et al.</td>
<td>2017</td>
<td>60</td>
<td>F</td>
<td>Liposuction</td>
<td>Autopsy</td>
<td>No</td>
<td>Not written</td>
<td>Not written</td>
</tr>
<tr>
<td>Scarpino M, et al.</td>
<td>2016</td>
<td>64</td>
<td>F</td>
<td>Empyema (treated by VATS)</td>
<td>MRI</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>May J, et al.</td>
<td>2016</td>
<td>57</td>
<td>F</td>
<td>Sickle-β + thalassemia, bone marrow necrosis</td>
<td>Clinical history, CT, MRI</td>
<td>No</td>
<td>Not written</td>
<td>No</td>
</tr>
<tr>
<td>Mendoza-Morales RC, et al.</td>
<td>2016</td>
<td>24</td>
<td>F</td>
<td>Gluteal injection of vitamin E (for cosmetic enhancement)</td>
<td>Autopsy</td>
<td>Yes*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kammeyer R, et al.</td>
<td>2016</td>
<td>54</td>
<td>F</td>
<td>Hemoglobin SC disease</td>
<td>MRI</td>
<td>No</td>
<td>Not written</td>
<td>No</td>
</tr>
<tr>
<td>Graff DM, et al.</td>
<td>2015</td>
<td>18</td>
<td>M</td>
<td>Hemoglobin SC disease, bone marrow necrosis</td>
<td>Autopsy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Celik SU, et al.</td>
<td>2015</td>
<td>33</td>
<td>F</td>
<td>Renal angiomyolipoma</td>
<td>CT</td>
<td>No</td>
<td>Not written</td>
<td>No</td>
</tr>
<tr>
<td>Schrufer-Poland T, et al.</td>
<td>2015</td>
<td>29</td>
<td>F</td>
<td>Arnold-Chiari malformation, Cesarean delivery</td>
<td>Autopsy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Alobeidi F, et al.</td>
<td>2015</td>
<td>8</td>
<td>F</td>
<td>Sickle cell disease, bone marrow necrosis</td>
<td>MRI</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Coronado-Malagón M, et al.</td>
<td>2010</td>
<td>26</td>
<td>F</td>
<td>Soft tissue filter injection</td>
<td>CT, BAL</td>
<td>No</td>
<td>Not written</td>
<td>Not written</td>
</tr>
<tr>
<td>Bilgrami S, et al.</td>
<td>1999</td>
<td>59</td>
<td>F</td>
<td>Diffuse large-cell lymphoma</td>
<td>Autopsy</td>
<td>No</td>
<td>Not written</td>
<td>Not written</td>
</tr>
<tr>
<td>Bilgrami S, et al.</td>
<td>1999</td>
<td>54</td>
<td>M</td>
<td>Diffuse large-cell lymphoma</td>
<td>Autopsy</td>
<td>No</td>
<td>Not written</td>
<td>Not written</td>
</tr>
<tr>
<td>Schulz F, et al.</td>
<td>1996</td>
<td>63</td>
<td>F</td>
<td>Acute hepatic necrosis with steatosis</td>
<td>Autopsy</td>
<td>No</td>
<td>Not written</td>
<td>No</td>
</tr>
<tr>
<td>Schulz F, et al.</td>
<td>1996</td>
<td>46</td>
<td>M</td>
<td>Acute hepatic necrosis caused by fulminant viral hepatitis with steatosis</td>
<td>Autopsy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rosen JM, et al.</td>
<td>1986</td>
<td>40</td>
<td>M</td>
<td>Diffuse mixed cellularity lymphoma</td>
<td>Biopsy, autopsy</td>
<td>No</td>
<td>Not written</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Gas chromatography coupled with mass spectrometry using oily material between the muscle fibers in buttock area. (tocopherol was detected).
REFERENCES


© 2017 Japanese Society of Pathology and John Wiley & Sons Australia, Ltd